

REMARKS

Claims 40, 42, 44, 46, 56-58, and 61 are presently pending. The Examiner has again maintained the obviousness rejections from the previous Office Action that are rebutted in the following order:

- I. Claims 40 and 61 are rejected under 35 USC §103(a) allegedly unpatentable over United States Patent No. 4,873,316 Meade et al., in view of Jorgensen et al., *J Biol Chem* 262:6729-6734 (1987), Seegers et al. *Blood* 5:421-433 (1950), and further in view of van Cott and Velander *Expert Opinion on Investigational Drugs* 7:1683-1690 (1998), and previously cited Velander et al. *Proc. Natl. Acad. Sci. USA* 89:12003-12007 (1992).
- II. Claims 40, 42, 44, 46, 56 and 58 are rejected under 35 USC §103(a) allegedly unpatentable over United States Patent No. 4,873,316 Meade et al., in view of Jorgensen et al., *J Biol Chem* 262:6729-6734 (1987), and further in view of Le Bonniec et al., *J Biochem* 266:137796-13803 (1991), and Velander et al. *Proc. Natl. Acad. Sci. USA* 89:12003-12007 (1992).
- III. Claims 40 and 57 are rejected under 35 USC §103(a) allegedly unpatentable over United States Patent No. 4,873,316 Meade et al. in view of Jorgensen et al., *J Biol Chem* 262:6729-6734 (1987), and further in view of Seegers et al., *Blood* 5:421-433 (1950); and further in view of Le Bonniec et al., *J Biochem* 266:137796-13803 (1991) and Velander et al. *Proc. Natl. Acad. Sci. USA* 89:12003-12007 (1992).

I. The Claims Are Not *Prima Facie* Obvious

Obviousness is currently determined based upon an evaluation of the magnitude of the differences between the claimed embodiment and the asserted prior art:

In *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966), the Court set out a framework for applying the statutory language of § 103 ... "Under § 103, the scope and content of the prior art are

to be determined; differences between the prior art and the claims at issue are to be ascertained ...

KSR v. Teleflex, 127 S. Ct. 1727, 1734 (2007). The Supreme Court in *KSR* identified a number of rationales to support a conclusion of obviousness which are consistent with the proper “functional approach” to the determination of obviousness as laid down in *Graham*:

The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit.

MPEP § 2143. It appears to the Applicants that the Examiner is attempting to argue one of *KSR*’s rationale encompassing that “combining prior art elements according to known methods to yield predictable results”. The Applicants present below an argument showing that the Examiner has not fulfilled the first requirement of this particular rationale:

Then, Office personnel must articulate the following:

- (1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference ...

MPEP § 2143 [emphasis added]. As argued below, none of the cited references disclose a milk composition derived from a transgenic mammal comprising a human prothrombin protein or amino acid sequence. As such, the reference combination provided by the Examiner fails to find each element claimed in the prior art. Consequently, the Examiner has not created a *prima facie* case of obviousness that ‘combines prior art elements according to known methods to yield predictable results’.

A. Claims 40 and 61 Are Not Obvious Under Meade, Jorgensen et al., Seegers et al., van Cott et al., and Velandier et al.

The Examiner has reasserted the same obviousness rejection as in the last Office Actions. The Applicants again disagree. Nonetheless, without acquiescing to the Examiner’s argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicants have amended Claim 40 to clarify that the ‘milk composition derived from a transgenic mammal’ comprises a “human prothrombin protein”. Further, Claim

40 has been amended to clarify that the prothrombin concentration is “at least 1.5 mg/ml”. See, *The Second Velander Declaration*. Unnecessary limitations of “a polypeptide” and “a completely γ -carboxylated Gla domain” have been deleted from Claim 40. As a result, Claim 42 has been amended to recite that a post-translational modification may be a γ -carboxylation. Claims 42 and 61 have been amended to maintain proper antecedent basis. Further, Claims 44 and 46 have been concomitantly canceled. These amendments are made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

The Applicants submit that a milk composition derived from a transgenic mammal comprising at least 1.5 mg/ml of a human prothrombin amino acid sequence is not found in the prior art. The Examiner is respectfully reminded that the courts have generally considered the biotechnological arts as ‘unpredictable’:

In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work.

MPEP § 2164.03 [emphasis added]. This judicial doctrine is relevant to the Applicant's presently claimed embodiment because it disallows a conclusory argument that an expression of a first recombinant protein makes obvious an expression of a second recombinant protein.

- 1. The References Do Not Include All The Applicant's Claimed Elements**
 - a. Meade et al. Does Not Include Prothrombin In Milk Derived From A Transgenic Mammal**

The Examiner states that:

The Examiner relied on Meade et al., for teaching an efficient means of making large quantities of recombinant protein in milk and that any protein may be produced using their method (Meade et al. cols 1-3 ...

Office Action mailed Sept 2009, pg 4. The Applicants disagree that this teaching has any relevancy to the Applicant's claimed embodiment. Meade et al. does not teach the expression of prothrombin into milk derived from a transgenic mammal at any concentration. In fact, Meade et al. does not even mention the term 'prothrombin'.

Further, Meade et al. uses the term "large quantities" only once in an attempt to frame a goal that has advantages of cell culture secretion of recombinant protein and makes no attempt to provide guidance to one having ordinary skill in the art as how to achieve *in vivo* expression of "large quantities" of recombinant protein. *Meade et al. col 1 ln 53-56.* In fact, Meade et al. is limited to teaching the expression of very small quantities of recombinant protein.

The G1 progeny produced 0.2-0.5 µg/ml of TPA in their milk.

Meade et al., col 7 ln 25-26 [emphasis added]. As such, Meade et al. only identified the problem of low expression in cell culture but failed to solve the problem:

This technique has proven be expensive and often unreliable due the variability of cell culture methods. For example, average yields are 10 mg of a milk recombinant protein per liter of culture media,

Meade et al., col. 1 ln 43-46. In fact, Meade et al. does not teach the expression of any recombinant protein at the Applicant's presently claimed concentrations. To this point, Meade et al. only teaches an expression level that is approximately one-thousand times lower than the Applicant's currently claimed embodiment.

Therefore, Meade et al. fails to teach prothrombin in milk derived from a transgenic mammal, such that the Applicant's currently claimed elements are unpredictable and surprising.

2. Jorgensen et al Does Not Include Prothrombin In Milk Derived From A Transgenic Mammal

The Examiner agrees that Jorgensen et al, also does not provide any teachings relevant for high expression of any recombinant protein (i.e., for example, prothrombin):

With regarding to Applicant indicating that Jorgensen et al. do not teach high levels of expression, Applicant is correct.

Office Action pg 6. Therefore, Jorgensen et al. fails to teach prothrombin in milk derived from a transgenic mammal, such that the Applicant's currently claimed elements are unpredictable and surprising.

**3. Seegers Does Not Include The Applicant's Claimed Prothrombin
Expression Concentration**

The Examiner states that:

Seegers et al. teach that activation of purified prothrombin is accomplished by dissolving the purified prothrombin in a 25% solution of sodium citrate ...

Office Action pg 7. Seegers provides no teaching of a milk composition derived from a transgenic mammal comprising a human prothrombin protein or amino acid sequence. Consequently, the Examiner has not shown that Seegers et al. remedies the above identified deficiencies of Meade et al. and Jorgensen et al..

Therefore, Seegers et al. fails to teach prothrombin in milk derived from a transgenic mammal, such that the Applicant's currently claimed elements are unpredictable and surprising.

**4. van Cott et al. Does Not Include Prothrombin In Milk Derived From
A Transgenic Mammal**

In response to the Applicant's previous argument that Van Cott et al. does not teach the expression of prothrombin, the Examiner rebuts that:

As indicated above, Meade et al., Jorgensen et al., and Velander et al. provide guidance for an artisan to make large amounts of recombinant prothrombin in the milk of mammals.

Office Action pg 6. The Applicants submit that this is a clear admission by the Examiner that Van Cott et al. does not disclose a milk composition derived from a transgenic mammal comprising a human prothrombin amino acid sequence. In fact, van Cott et al. does not even mention the term 'prothrombin'.

The arguments herein also show that Meade et al. Jorgensen et al., and Velander also do not disclose this claimed element such the Examiner's rebuttal is insufficient upon which to maintain an obviousness rejection. In fact, as argued before, van Cott et al. does not even mention prothrombin as a possible protein for expression. Nevertheless, the prothrombin expression level now recited in Claim 40 is more than 5 times superior to the Protein C expression referred to in van Cott et al. (i.e., 0.1 g/l/h = 0.1 mg/ml/h).

Therefore, Seegers et al. fails to teach prothrombin in milk derived from a transgenic mammal, such that the Applicant's currently claimed elements are unpredictable and surprising.

**5. Velander et al. Does Not Include the Applicant's Claimed
Prothrombin Expression Concentration**

The Examiner further asserts Velander et al. for allegedly fulfilling the above deficiencies of Meade et al. and Jorgensen et al.:

... the Examiner relied upon Velander et al., who teach that recombinant protein can be expressed in milk of transgenic pigs at levels as high as 1000 $\mu\text{g/ml}$ (i.e., 1 mg/ml)(Velander et al. page 12005, 1st col, parag. Under "Protein Analysis", see also Figure 1).

Office Action mailed Sept. 2009, pg 4-5. The Applicants disagree and respectfully point out that Velander et al. does not disclose a milk composition derived from a transgenic mammal comprising a human prothrombin protein or amino acid sequence. In fact, Velander et al. does not even mention the term 'prothrombin'. As such, the Protein C data within Velander et al. has no relevancy regarding the expression of prothrombin from a transgenic mammal.

Therefore, Velander et al. fails to teach prothrombin in milk derived from a transgenic mammal, such that the Applicant's currently claimed elements are unpredictable and surprising.

6. Conclusion

When Meade et al., Jorgensen et al., Seegers et al., van Cott et al., and Velander et al. are taken in combination, the Applicants submit that the Examiner has not created a *prima facie* case of obviousness against Claims 40 and 61. In particular, the combined references do not teach all the Applicants' claimed elements. For example, the Applicants have shown above the this reference combination does not disclose a milk composition derived from a transgenic mammal containing a human protein amino acid sequence at a concentration of at least 1.5 mg/ml.

The Applicants superior and advantageous results overcome the Examiner's obviousness argument. The Applicants respectfully request that the Examiner withdraw the present rejection.

II. Claims 40, 42, 44, 46, 56 and 58 Are Not Obvious Under Meade et al., Jorgensen et al., Le Bonniec et al., And Velander et al.

The Applicants respond to this rejection by incorporating by reference the arguments presented regarding Meade et al. Jorgensen et al., and Velander et al. in Section I, above. The Examiner has not found that Le Bonneic et al. discloses a milk composition derived from a

transgenic mammal containing a human protein amino acid sequence at a concentration of at least 1.5 mg/ml.

The Applicants superior and advantageous results overcome the Examiner's obviousness argument. The Applicants respectfully request that the Examiner withdraw the present rejection.

III. Claims 40 and 57 Are Not Obvious Under Meade et al., Jorgensen et al., Seegers et al., Le Bonniec et al., and Velander et al.

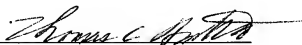
The Applicants respond to this rejection by incorporating by reference the arguments presented regarding Meade et al. Jorgensen et al., Seegers et al., and Velander et al. in Section I, above. The Examiner has not found that Le Bonniec et al. discloses a milk composition derived from a transgenic mammal containing a human protein amino acid sequence at a concentration of at least 1.5 mg/ml.

The Applicants superior and advantageous results overcome the Examiner's obviousness argument. The Applicants respectfully request that the Examiner withdraw the present rejection.

CONCLUSION

The Applicants believe that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that all grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned collect at 781-828-9870.

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By: 
Thomas C. Howerton
Reg. No. 48,650

Medlen & Carroll, LLP
101 Howard Street, Ste. 350
San Francisco, CA 94105
781-828-9870